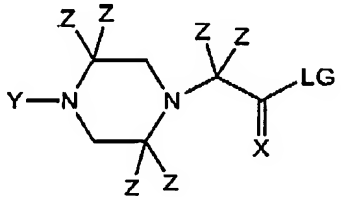
RECEIVED
CENTRAL FAX CENTER
SEP 26 2006

3. **In the Claims**

PLEASE ENTER THE FOLLOWING AMENDMENT WITHOUT PREJUDICE OR DISCLAIMER.

1. (Original) An N-substituted piperazine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester;

X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms;

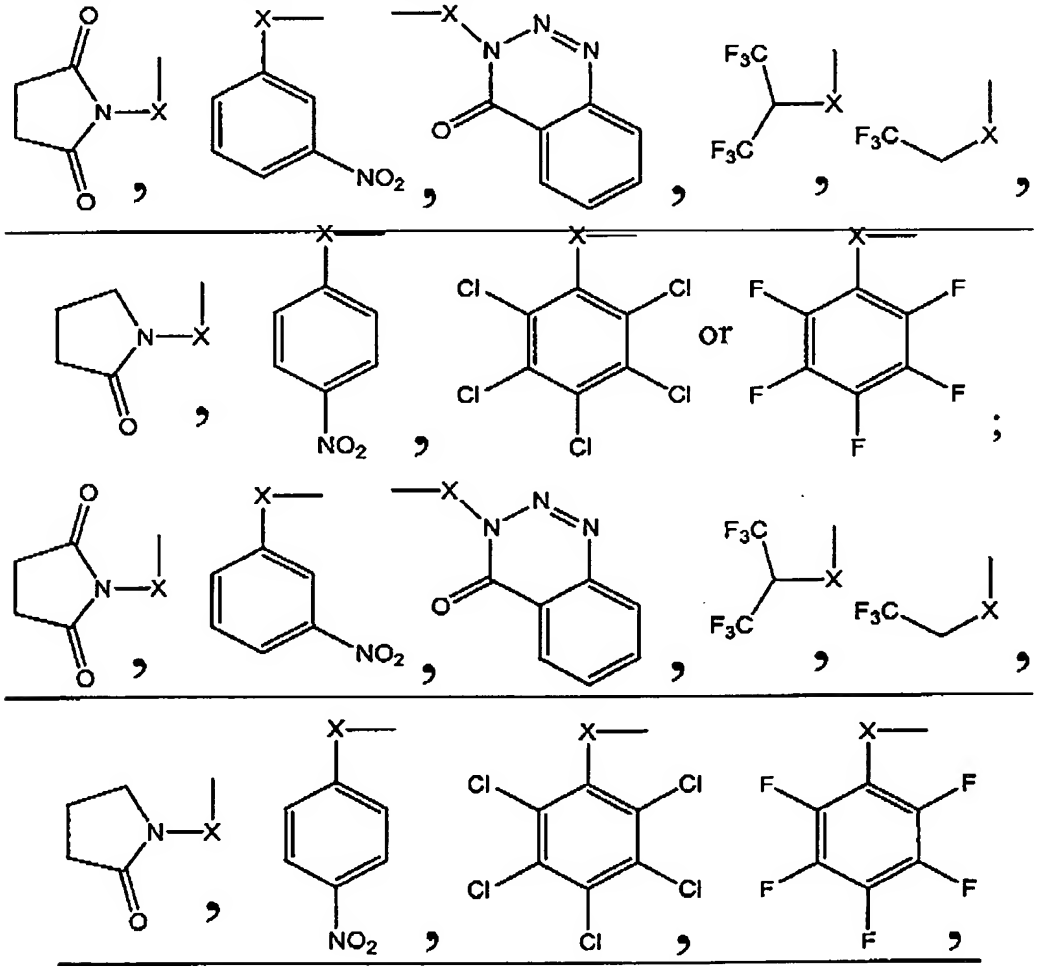
each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

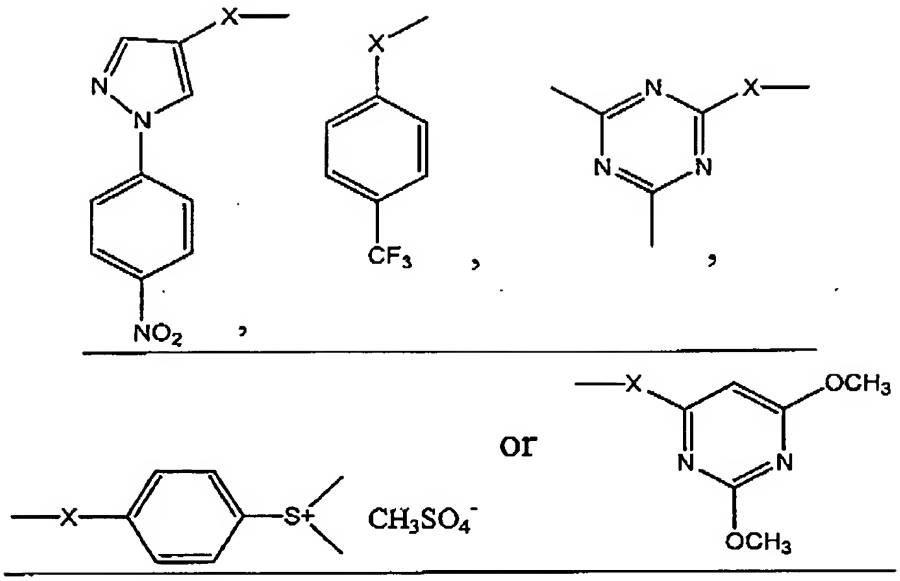
optionally the N-substituted piperazine acetic acid active ester comprises one or more heavy atom isotopes.

2. (Original) The compound of claim 1, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

3. (Original) The compound of claim 1, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

4. (Currently Amended) The compound of claim 1, wherein LG is:





and wherein X is O or S.

5. (Canceled)

6. (Original) The compound of claim 1, wherein LG is N-hydroxysuccinimide.

7. (Original) The compound of claim 1, wherein each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

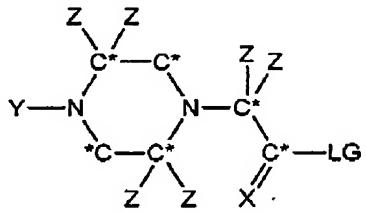
8. (Original) The compound of claim 1, wherein each Z is independently hydrogen, methyl or methoxy.

9. (Original) The compound of claim 1, wherein Y is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl.

10. (Original) The compound of claim 1, wherein X is ^{16}O or ^{18}O.

11. (Original) The compound of claim 1, wherein each nitrogen atom of the piperazine ring is independently ^{14}N or ^{15}N.

12. (Original) The compound of claim 1 of the formula:



wherein

each C* is independently ^{12}C or ^{13}C;

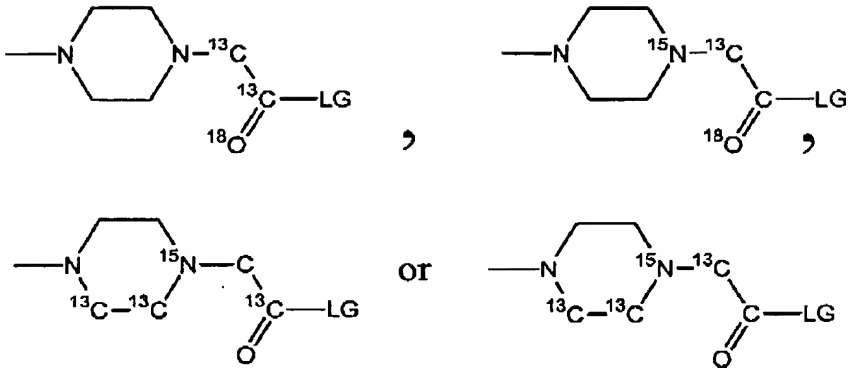
LG is the leaving group of an active ester;

X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

13. (Original) The compound of claim 2 of the formula:



wherein, LG is the leaving group of an active ester.

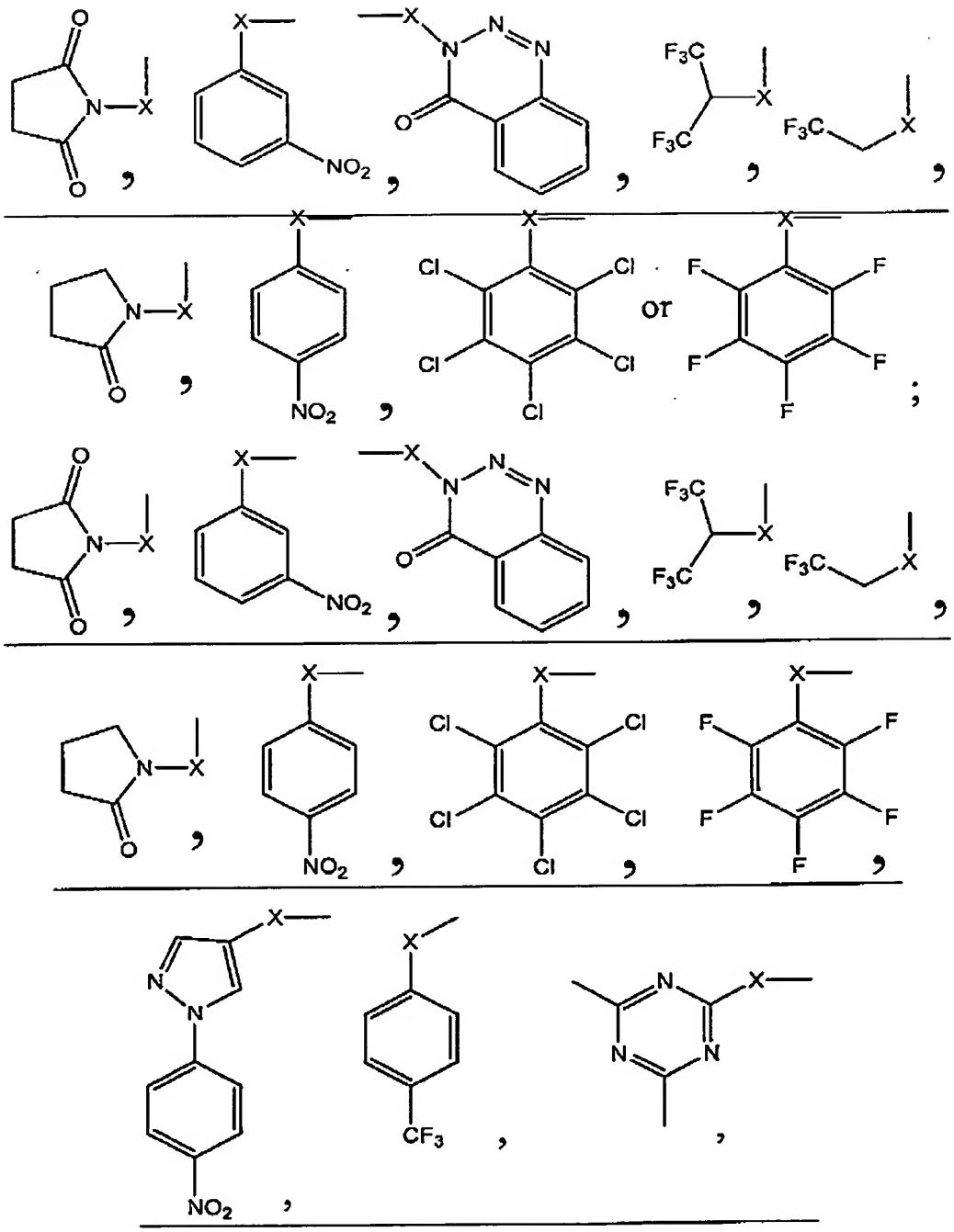
14. (Original) The compound of claim 13, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.

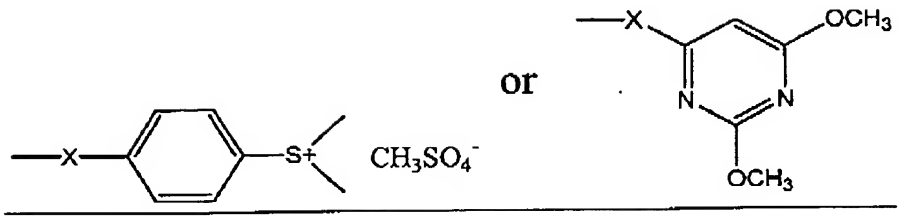
15. (Currently Amended) The compound of claim 13, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity, in at least 93 percent or isotopic purity or in at least 96 percent or isotopic purity.

Claims 16-17 (Canceled)

18. (Original) The compound of claim 13, wherein LG is N-hydroxysuccinimide.

19. (Currently Amended) The compound of claim 13, wherein LG is:





and wherein X is O or S.

20. (Canceled)

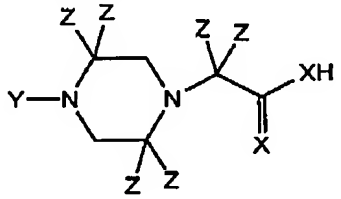
21. (Original) The compound of claim 1, wherein the N-substituted piperazine acetic acid active ester is a mono-TFA salt, a mono-HCl salt, a bis-HCl salt or a bis-TFA salt.

22. (Currently Amended) The compound of claim 2, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity, in at least 93 percent isotopic purity or in at least 96 percent isotopic purity.

Claims 23-24 (Canceled)

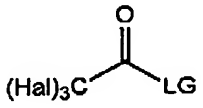
25. (Withdrawn – Currently Amended) A method comprising:

reacting an N-substituted piperazine acetic acid compound of the formula:

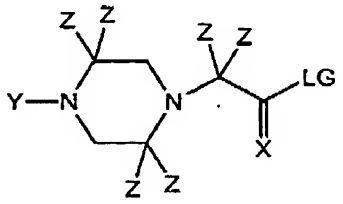


or a salt thereof,

with: 1) a compound of the formula:



and, if the piperazine acetic acid compound is a salt, 2) optionally with a base strong enough to deprotonate the basic nitrogen atoms of the piperazine ring; to thereby form an N-substituted piperazine acetic acid active ester of the formula:



or a salt thereof, wherein;

Hal is a fluorine, chlorine, bromine or iodine;

LG is the leaving group of an active ester;

X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

optionally the N-substituted piperazine acetic acid moiety comprises one or more heavy atom isotopes; and

optionally treating the N-substituted piperazine acetic acid active ester with an acid.

26. (Withdrawn) The method of claim 25, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

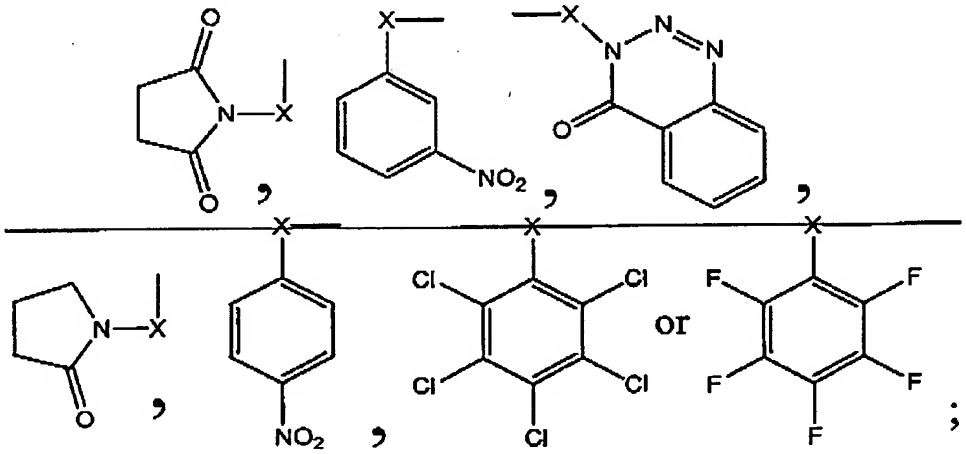
27. (Withdrawn) The method of claim 25, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

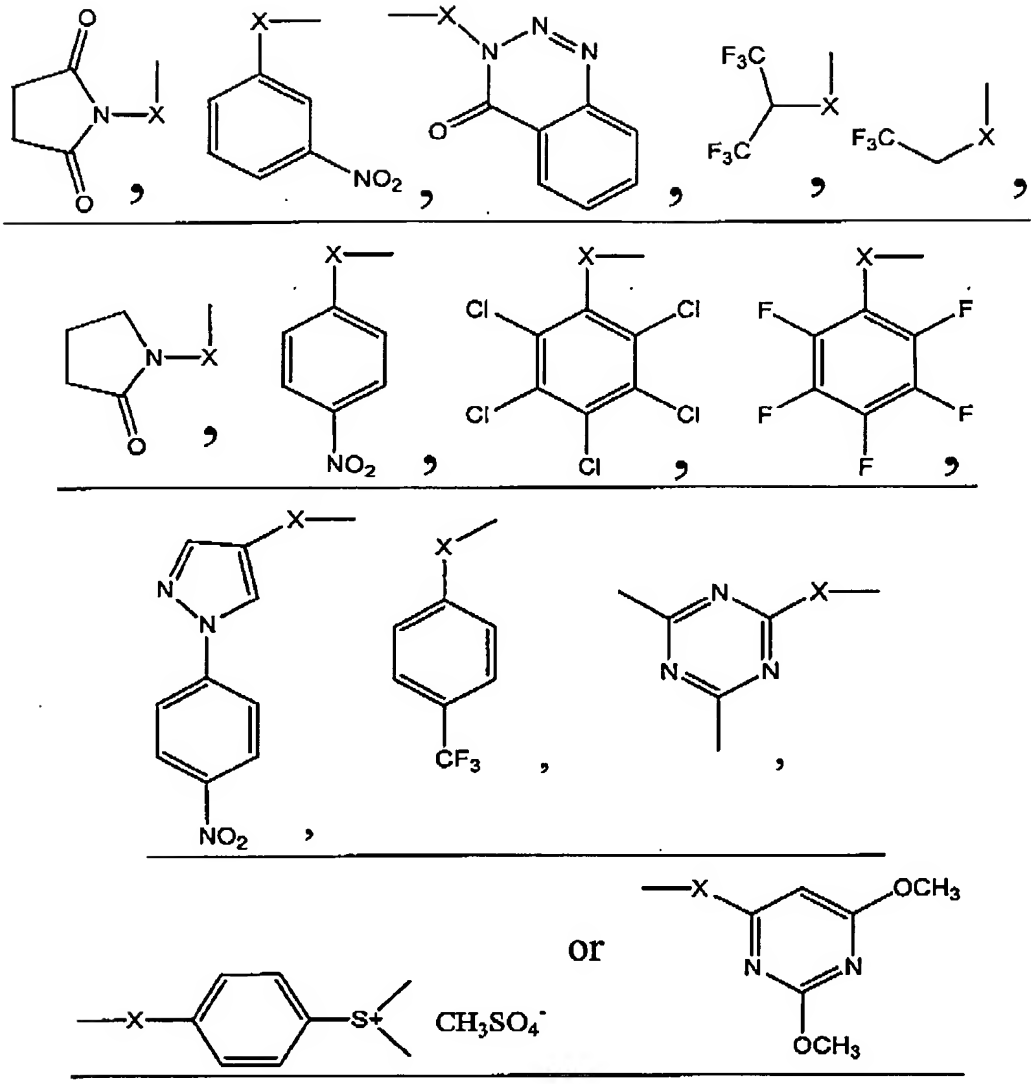
28. (Withdrawn) The method of claim 25, wherein the acid is HCl or TFA.

29. (Withdrawn - Currently Amended) The method of claim 26, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity, in at least 93 percent isotopic purity or in at least 96 percent isotopic purity.

Claims 30-31 (Canceled)

32. (Withdrawn – Currently Amended) The method of claim 25, wherein LG is:





and wherein X is O or S.

33. (Canceled)

34. (Withdrawn) The method of claim 25, wherein LG is N-hydroxysuccinimide.

35. (Withdrawn) The method of claim 25, wherein each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

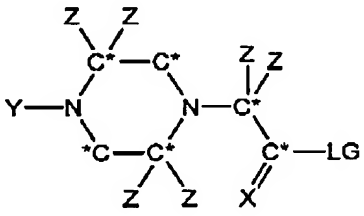
36. (Withdrawn) The method of claim 25, wherein each Z is independently hydrogen, methyl or methoxy.

37. (Withdrawn) The method of claim 25, wherein Y is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl.

38. (Withdrawn) The method of claim 25, wherein X is ^{16}O or ^{18}O.

39. (Withdrawn) The method of claim 25, wherein each nitrogen atom of the piperazine ring is independently ^{14}N or ^{15}N.

40. (Withdrawn) The method of claim 25, wherein the compound to be reacted has the formula:



wherein,

each C* is independently ^{12}C or ^{13}C;

LG is the leaving group of an active ester;

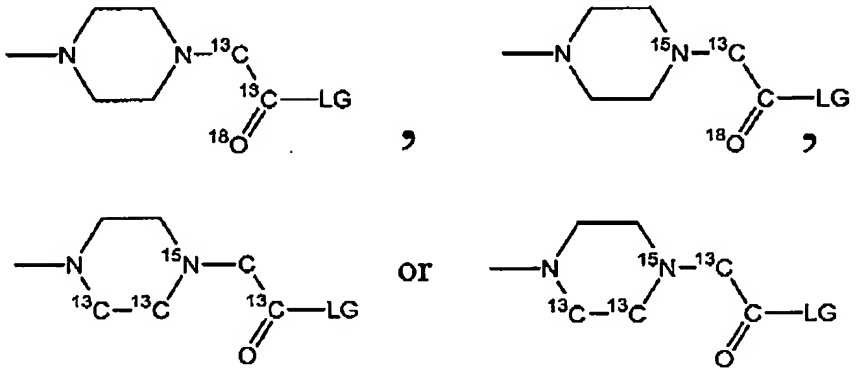
X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms, a

straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

41. (Withdrawn – Currently Amended) The method of claim ~~23~~ 25, wherein the product of the reaction is an N-methyl piperazine acetic acid active ester of the formula:

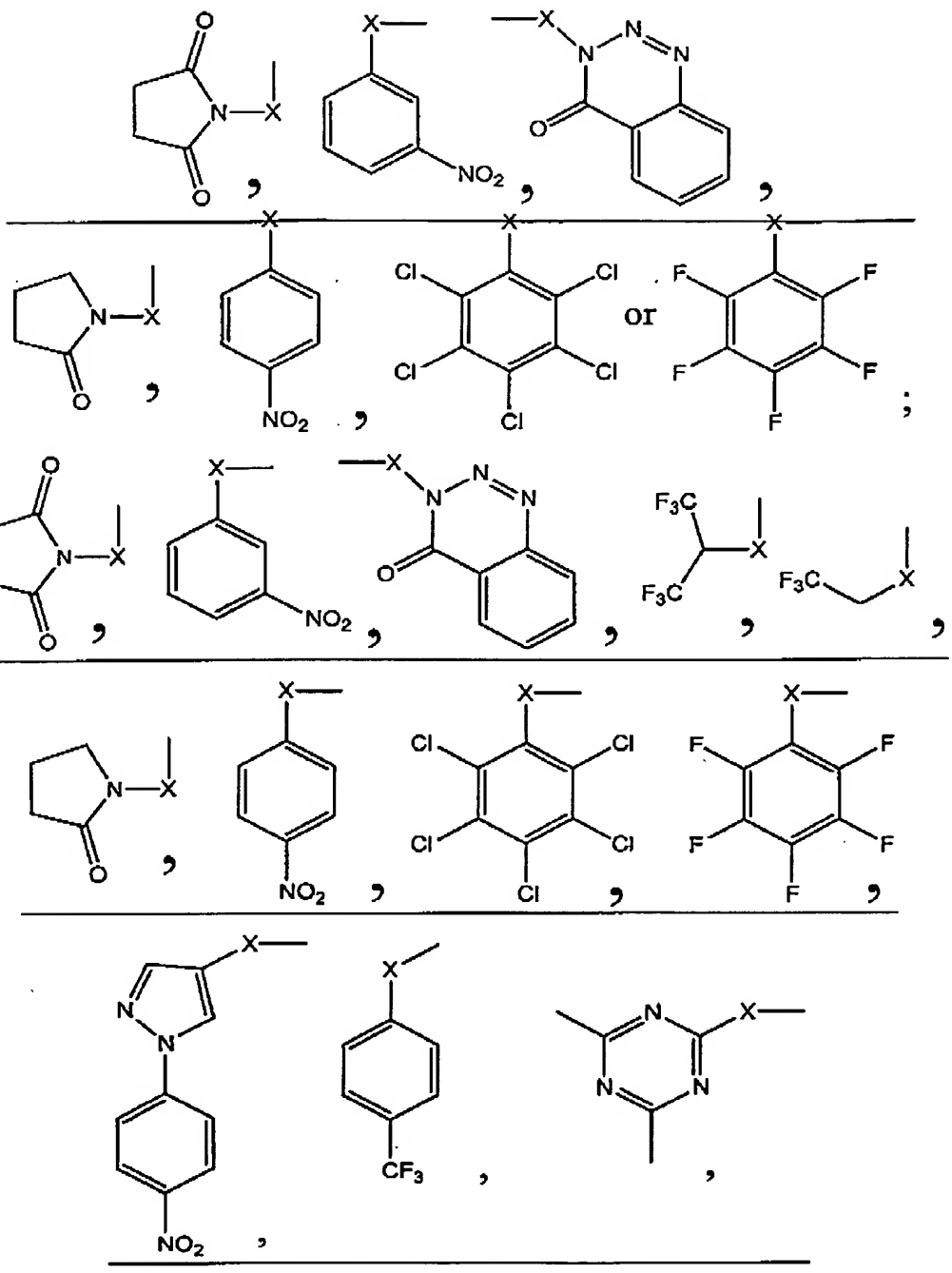


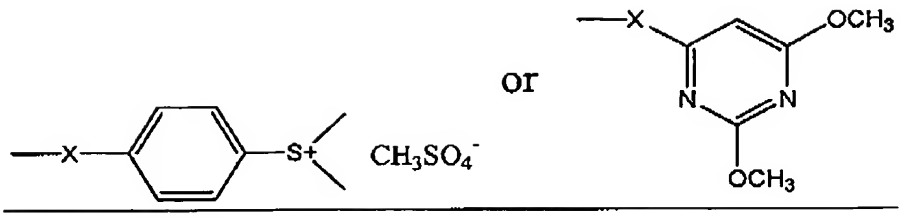
wherein, LG is the leaving group of an active ester.

42. (Withdrawn – Currently Amended) The method of claim 41, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity, in at least 93 percent isotopic purity or in at least 96 percent isotopic purity.

Claims 43-44 (Canceled)

45. (Withdrawn – Currently Amended) The method of claim 41, wherein LG is:





and wherein X is O or S.

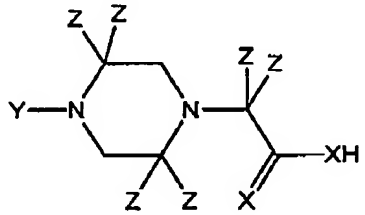
46. (Canceled)

47. (Withdrawn) The method of claim 41, wherein LG is N-hydroxysuccinimide.

48. (Withdrawn) The method of claim 41, wherein the N-substituted piperazine acetic acid active ester is a mono-TFA salt, a mono-HCl salt, a bis-HCl salt or a bis-TFA salt.

49. (Withdrawn) The method of claim 25, wherein the N-substituted piperazine acetic acid active ester is a mono-TFA salt, a mono-HCl salt, a bis-HCl salt or a bis-TFA salt.

50. (New) An isotopically enriched N-substituted piperazine acetic acid compound of the formula:



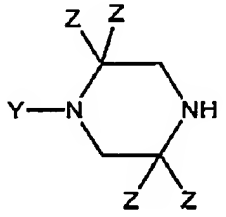
, or a salt thereof, comprising one or more heavy atom isotopes, wherein;

X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

51. (New) An isotopically enriched N-substituted piperazine compound of the formula:



, or a salt thereof, comprising one or more heavy atom isotopes, wherein;

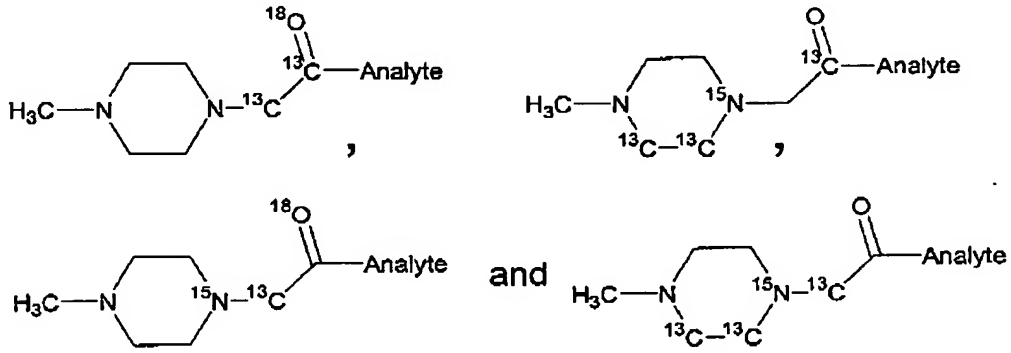
Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms; and

each Z is independently hydrogen, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or

unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms;

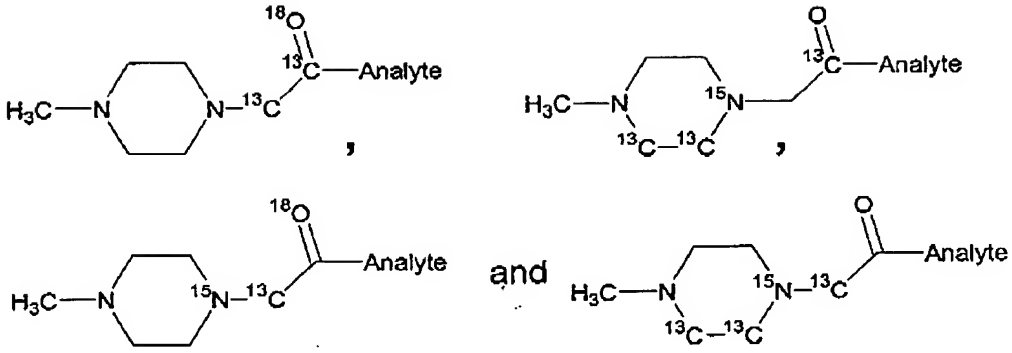
wherein the N-methyl piperazine is isotopically enriched with either of ^{13}C and/or ^{15}N.

52. (New) A mixture comprising the same analyte labeled with two or more different isobaric labels, wherein at least two of the labeled analytes are compounds of the formula selected from the group consisting of:



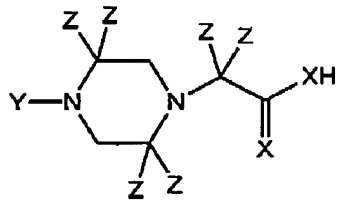
or a salt thereof.

53. (New) A mixture of fragment ions of the same analyte labeled with two or more different isobaric labels selected for fragmentation and further analysis in a tandem mass spectrometer, wherein at least two of the labeled analytes are compounds of a formula selected from the group consisting of:



wherein all ion fragments are either positively or negatively charged.

54. (New) A compound of formula:



including all possible salt forms thereof, wherein the compound represents all possible isotopically enriched N-substituted piperazine acetic acids comprising one or more heavy atom isotopes;

wherein,

X is O or S;

Y is a straight chain or branched C1-C6 alkyl group or a straight chain or branched C1-C6 alkyl ether group wherein the carbon atoms of the alkyl group or alkyl ether group each independently comprise linked hydrogen, deuterium or fluorine atoms; and

each Z is independently hydrogen, fluorine, chlorine, bromine, iodine, an amino acid side chain, a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms, a straight chain or branched C1-C6 alkyl ether group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the

alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms or a straight chain or branched C1-C6 alkoxy group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen or fluorine atoms.